

The New Antibiotics

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Infectious Disease Service

The New Antibiotics

- Synercid
- Linezolid
- Cefipime
- Meropenem
- The Quinolones
- Cidofovir
- Zanamivir/Oseltamivir
- Abacavir/Amprenavir/Efavirenz

Synercid

- Quinupristin/dalfopristin
- Fixed 30:70 ratio
- Streptogramin antibiotic (isolated from *Streptomyces* sp.)
- Weak individual activity, but synergistic together

Synercid

- Mechanism of Action
 - inhibits bacterial protein synthesis by irreversibly binding to different sites on the 50S bacterial ribosomal subunit
 - quinupristin inhibits peptide chain elongation
 - dalfopristin interferes with peptidyl transferase

Synercid

- Mechanism of resistance
 - plasmid-mediated target modification
 - confers resistance to macrolides, lincosamides and quinupristin by methylation of their common binding site
 - drug-modifying enzymes or efflux

Synercid

- Antimicrobial activity
 - *E. faecium* (not *E. faecalis*)
 - bacteriostatic or slowly bactericidal
 - *S. aureus* (including MRSA)
 - CNS
 - *S. pneumoniae* (including PCN resistant)
 - viridans strep and Group A Strep
 - Legionella, *M. pneumoniae*

Synercid

- Administration
 - 7.5 mg/kg IV every 8-12 hours
- Distribution
 - does not penetrate CNS
 - eliminated primarily in bile
- Toxicities
 - phlebitis (75% when given through peripheral IV)
 - arthralgias/myalgias
 - hyperbilirubinemia (primarily conjugated)

Synercid

- Drug interactions
 - cyclosporin
 - antihistamines
 - NNRTIs and PIs
 - benzodiazepines
 - calcium channel blockers
 - HMG-CoA reductase inhibitors
 - cisapride
 - methylprednisolone, carbamazepine

Synercid

- Major uses
 - primarily multiple-drug-resistant gram-positive pathogens (VRE, MRSA)
 - VRE
 - 90% clearance of bacteremia
 - 52% overall efficacy (clinical success and eradication of initial pathogen)
 - Complicated skin and skin structure infections
 - equal to oxacillin and cefazolin

Linezolid

(not yet FDA approved)

- Available at WRAMC through ID protocol
- Unique class of synthetic antibacterial agents: oxazolidinones
- Mechanism of Action
 - inhibit protein synthesis (bacteriostatic)
 - bind to the 50S ribosome near the 30S ribosome interface
 - prevents initiation of protein synthesis

Linezolid

- Gram-positive organisms
 - VRE, MRSA, PCN-resistant *S. pneumo*
 - Significant gram-positive anaerobic effect
- Pharmacology
 - Can be given orally or IV (600 mg bid)
- Side-effects
 - tongue discoloration
 - HA (6.5%), diarrhea (8.3%), nausea (6.2%)
 - weak inhibitor of MAOI (not clinically relevant)

Linezolid

- Efficacy
 - 7 Phase III trials
 - Community-acquired pneumonia
 - Skin and soft-tissue infections
 - MRSA infections
 - Hospital-acquired pneumonia (with aztreonam or an aminoglycoside)
 - VRE infections

Cefepime

- Weaknesses of third-generation cephalosporins
 - ceftriaxone: *P. aeruginosa*
 - ceftazidime:
 - gram-positives (especially staphylococci and *S. pneumoniae*)
 - rising gram-negative resistance
 - cefepime: new “fourth” generation cephalosporin

Cefepime

- Uniquely broad activity against Enterobacteriaceae and *P. aeruginosa*, as well as *H. influenzae* and *Neisseria* sp.
 - rapid penetration through outer membrane (less time for *B*-lactamase effect)
 - high affinity for PBPs
 - stable to variety of *B*-lactamases

Cefepime

- 75% Enterobacteriaceae resistant to ceftazidime remain sensitive to cefepime
- MSSA, *S. pneumo* and other strep
- Poor activity against MRSA and enterococcus

Cefepime

- Clinical use
 - equal to ceftaz in nosocomial pneumonia and neutropenic fever
 - equal to ceftriaxone in severe CAP
 - So....
 - reserve for empirical therapy for nosocomial infections in which highly resistant organisms are anticipated

Meropenem

- Carbapenem
- Excellent penetration into bacteria, high affinity for PBPs and stability to B-lactamases
- Slightly more active than imipenem against gram-negative organisms
- Slightly less active than imipenem against gram-positive organisms

Meropenem

- Less epileptogenic and nephrotoxic than imipenem
- Clinical use:
 - nosocomial pathogens where imipenem would be used, but risk of seizures or nephrotoxicity is a concern

Quinolones

- Ciprofloxacin
- Norfloxacin
- Enoxacin
- Ofloxacin
- Pefloxacin
- Lomefloxacin
- Fleroxacin
- Sparfloxacin
- Levofloxacin
- Grepafloxacin
- Trovafloxacin
- Gatifloxacin
- Moxifloxacin

Quinolones

- Aerobic gram-negative bacilli
- Cipro: most potent against gram-negatives
- Trovafloxacin, gatifloxacin, moxifloxacin have increased potency against anaerobes
- Most newer agents with enhanced gram-positive coverage (*S. pneumoniae*)

Quinolones

- Sparfloxacin: photosensitivity/QT lengthening
- Gatifloxacin:
 - less active than cipro against gram-negatives
 - more active against gram-positives/anaerobes
 - 2-4x levofloxacin against *S. pneumo*
 - qd dosing

Cidofovir

- Nucleotide analogue of deoxycytidine monophosphate
- Inhibitory for acyclovir-resistant TK-deficient HSV and ganciclovir-resistant CMV
- Toxicity
 - nephrotoxicity (50% proteinuria, 15% elevated creatinine)
 - neutropenia (20%)

Cidofovir

- Clinical uses:
 - CMV retinitis
 - acyclovir-resistant HSV
 - ?PML
- Dosing
 - 5mg/kg q week for 2 weeks, then every other week
 - probenecid/saline

Zanamivir and Oseltamivir

- Neuraminidase inhibitors
 - neuraminidase cleaves terminal sialic acid residues on surfaces of host cells and influenza virus envelopes (promotes the release of viruses from infected cells)
 - results in viral aggregation and reduction in amount of virus released
 - treat both influenzae A and B

Zanamivir/Osetamivir

- Treatment
 - within 2 days of symptoms
 - reduce by ~1 day duration of moderate or severe symptoms (in patient with fever)
 - prevention of serious complications has not been demonstrated
- Prophylaxis
 - not FDA approved

Zanamivir/Osetamivir

- Dose
 - zanamivir: 2 inhalations bid for 5 days
 - oseltamivir: 75 mg po bid for 5 days
- Side-effects
 - zanamivir: RAD/COPD---bronchospasm
 - oseltamivir: GI
- Uses
 - ?better than rimantadine (more expensive)

New HIV Drugs

- Abacavir (Ziagen)
 - nucleoside analogue
 - with AZT/3TC (“triple nuke” regimen)
 - hypersensitivity reaction (2-3%)
- Amprenavir (Agenerase)
 - protease inhibitor
 - GI side-effects/rash
- Efavirenz (Sustiva)
 - non-nucleoside reverse transcriptase inhibitor
 - rash (15%), CNS, teratogenic